# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>PD/4-32802A | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2004/003511 | International filing date *(day/month/year)*<br>02.04.2004 | Priority date *(day/month/year)*<br>04.04.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/00 | | |
| Applicant<br>NOVARTIS AG et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 07.10.2004 | 04.07.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Borst, M<br>Telephone No. +49 89 2399-8648 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003511

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-14 as originally filed

   **Claims, Numbers**

   1-6 received on 15.04.2005 with letter of 12.04.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3

because:

☒ the said international application, or the said claims Nos. 3 (no examination as to industrial appliacbility only) relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-6 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-6 |
| Industrial applicability (IA) | Yes: | Claims | 1,2,4-6 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

**Subject-matter excluded from international preliminary examination (Rule 67.1(iv) PCT)**

Claim 3 is directed to a method for the treatment of the human or animal body by therapy and, thus, relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated under Section V with respect to industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

## Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

### I. Documents (D) considered to be relevant to novelty and inventive step

**D1:** WO 02/098376 A1 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN; KANG, SEWON; VOORHEES, JOHN) 12 December 2002 (2002-12-12)

**D2:** KOKELJ F ET AL: "Efficacy of cyclosporine plus etretinate in the treatment of erythrodermic psoriasis (three case reports)." JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY : JEADV. SEP 1998, vol. 11, no. 2, September 1998 (1998-09), pages 177-179, XP002315676 ISSN: 0926-9959

**D3:** CHAIDEMENOS G C ET AL: "Combination of cyclosporin A and acitretin in resistant erythrodermic psoriasis" JEADV. JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 11, September 1998 (1998-09), pages S290-S291, XP004556159 ISSN: 0926-9959

**D4:** TUYP E ET AL: "COMBINATION THERAPY FOR PSORIASIS WITH METHOTREXATE AND ETRETINATE" JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, vol. 14, no. 1, 1986, pages 70-73, XP009043274 ISSN: 0190-9622

**D5:** SINGH F ET AL: "ORAL TAZAROTENE AND ORAL PIMECROLIMUS: NOVEL ORAL THERAPIES IN DEVELOPMENT FOR PSORIASIS" JOURNAL OF DRUGS IN DERMATOLOGY, STRATEGIC COMMUNICATION IN DERMATOLOGY, NEW YORK, NY, US, vol. 3, no. 2, March 2004 (2004-03), pages 141-143, XP009039266 ISSN: 1545-9616

The numbering will be adhered to in the rest of the procedure.

1. **Novelty (Article 33(2) PCT)**
By restricting the independent claims to 33-epichloro-33-desoxyascomycin novelty appears to be established over D1-D4.

1.1. D1 (claim 1) discloses the combination of an immunosuppressant, one of which is ASM 981 (33-epichloro-33-desoxyascomycin) with a second active agent one of which is a retinoid for the treatment of acne. The combination of 33-epichloro-33-desoxyascomycin with retinoid can be arrived at after a double selection only.

1.2. D2 (page 179, paragraph entitled "2. Discussion") as well as D3 (S290-S291 P446) disclose the combination of cyclosporin and etetrinate/acitretin for the treatment of psoriasis. D4 (page 72-73, paragraph entitled "Comment") discloses the combination of methotrexate and etretinate for the treatment of psoriasis.
D2-D4 are silent as to 33-epichloro-33-desoxyascomycin.

2. **Inventive step (Article 33(3) PCT)**
The subject-matter of present claims 1-6 does not involve an inventive step.
It has been shown with the application on file (table on page 7) that the combination of 33-epichloro-33-desoxyascomycin and tazarotene provides an increased antiinflammatory effect in experimental ACD (acute allergic contact dermatitis) compared to monotherapy.
It was known from the closest prior art D2-D4 that the combination of different immunosuppressive agents, such as methotrexate or cyclosporin A, with retinoids, such as etetrinate or acitretin, provides an improved therapeutic effect in the treatment of psoriasis compared to monotherapy.
The objective technical problem to be solved with the application on file was to provide an alternative synergistic combination therapy for the treatment of dermatological disorders.
In view of the known activity of the immunosuppressive agent 33-epichloro-33-desoxyascomycin in the treatment of psoriasis (cf. D5: page 142-143), it was obvious to combine this agent with retinoids and, thus, to arrive at the subject-matter of the claims on file. This is true, in particular because it cannot be derived from the application on file whether and how pimecrolimus differs from the immunosuppressive agents listed in the application, and particularly from methotrexate or cyclosporin A, for which the synergism was known from the prior art.

## II. P-documents (P) (Rule 64.1(b) PCT)

CONNELLY E A ET AL: "Treatment of facial angiofibromas with topical pimecrolimus and tazarotene gel." JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 121, no. 1, July 2003 (2003-07), page 0030, XP009043277 & INTERNATIONAL INVESTIGATIVE DERMATOLOGY 2003 : JOINT MEETING OF THE EUROPEAN SOCIETY FOR DERMATOLOGI; MIAMI BEACH, FLORIDA, USA; APRIL 30-MAY 04, 2003 ISSN: 0022-202X

The priority appears to be validly claimed for the independent claims on file. Therefore the above document does not constitute prior art within the meaning of Rule 64.1(b) (P-doc).

**Claims:** amended April-2005

1. A pharmaceutical composition comprising 33-epichloro-33-desoxyascomycin in combination or association with a retinoid, together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 wherein the retinoid is etretinate, isotretinoin or tazarotene.

3. A method of treatment of a dermatological disease such as eczema, atopic dermatitis, acne, psoriasis, skin aging, sun damage, post-peel erythema or stretch marks in a subject suffering from or at risk for such condition, comprising co-administering an additive/synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition according to claim 1 comprising mixing 33-epichloro-33-desoxyascomycin and a retinoid, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising 33-epichloro-33-desoxyascomycin and a retinoid in separate unit dosage forms, together with instructions for use.

6. A composition according to claim 1 or 2 comprising a further pharmaceutically active agent which is an antibacterial.